Fiber, sex, and colorectal adenoma: results of a pooled analysis[1–3]

Elizabeth T Jacobs, Elaine Lanza, David S Alberts, Chiu-Hsieh Hsu, Ruiyun Jiang, Arthur Schatzkin, Patricia A Thompson, and María Elena Martínez

ABSTRACT

Background: Evidence for an association between dietary fiber and colorectal neoplasia has been equivocal, and some data suggest that there may be sex differences in response to fiber.

Objective: We sought to determine whether fiber affects colorectal adenoma recurrence differently in men and women by combining the study populations of 2 large clinical intervention trials: the Wheat Bran Fiber Trial and the Polyp Prevention Trial.

Design: Data from 3209 participants combined from 2 trials were analyzed with logistic regression models to examine the effect of a dietary intervention on colorectal adenoma recurrence in the pooled population as a whole and by sex.

Results: The adjusted odds ratio for adenoma recurrence for those in the intervention group of either the Wheat Bran Fiber Trial or the Polyp Prevention Trial was 0.91 (95% CI: 0.78, 1.06). For men, the intervention was associated with statistically significantly reduced odds of recurrence with an odds ratio of 0.81 (95% CI: 0.67, 0.98); for women, no significant association was observed. Using a likelihood-ratio test, we found a statistically significant interaction between intervention group and sex ($P = 0.03$).

Conclusion: The results of the current analyses indicate that men may experience more benefit from dietary fiber than do women and may help to explain some of the discrepant results reported in the literature. *Am J Clin Nutr* 2006;83:343–9.

KEY WORDS Dietary fiber, sex, colorectal adenoma, fiber intervention, colorectal neoplasia, Wheat Bran Fiber Trial, Polyp Prevention Trial

INTRODUCTION

On the basis of low rates of colon cancer in Africa, where high quantities of fiber are consumed (1), Burkitt proposed in 1971 that high dietary fiber intake might protect against this malignancy. Since that time, there has been a great deal of investigation into the potential protective effect of fiber on colorectal neoplasia. Many correlational and case-control epidemiologic studies have supported a protective effect of fiber on colorectal neoplasia (2–8); however, several prospective studies have yielded equivocal results (9–12). Furthermore, the results of 2 large randomized clinical trials failed to show protection from recurrent adenomas with increased fiber contents, decreased fat contents, or both in the diet (13, 14). In the Polyp Prevention Trial (PPT), there was no reduction in risk of colorectal adenoma recurrence with the consumption of a low-fat, high-fiber diet (14). In the Wheat Bran Fiber (WBF) Trial, there was no difference in the rate of recurrent adenomatous polyps between those randomly assigned to consume a high-fiber supplement and those in the low-fiber group (13). More recently, reports from 2 large observational investigations found that increased fiber intake was significantly associated with a reduced risk of colorectal adenomas (15) and cancer (16). Thus, the relation between fiber and colorectal neoplasia remains controversial. Of interest, results from both the WBF trial and the PPT suggest that there may be a sex difference with regard to the effect of the interventions tested (13, 14) and that the amount of fiber consumption at baseline might also have affected the results (17). We had the unique opportunity to pool data from the WBF trial and the PPT—2 large, well-conducted clinical trials that both included an intervention aimed at adding fiber to the diet to determine whether fiber had different effects in men and women.

SUBJECTS AND METHODS

Subjects

Data from participants in the WBF trial and the PPT were pooled to conduct the current analyses. The design and results of these trials were described in detail in the literature (18, 19), and a brief description of each trial is included below.

Wheat Bran Fiber Trial

The WBF trial was conducted at the University of Arizona to assess whether the consumption of a high-fiber cereal supplement reduces the risk of adenoma recurrence compared with a low-fiber supplement. Study participants were patients who had recently had a colorectal adenoma removed at colonoscopy. Participants were randomly assigned to receive either 13.5 or 2.0 g

[1] From the Arizona Cancer Center (ETJ, DSA, C-HH, RJ, and MEM), the Mel and Enid Zuckerman Arizona College of Public Health (ETJ, DSA, C-HH, and MEM), the College of Medicine (DSA), and the Department of Pathology (PAT), University of Arizona, Tucson, AZ, and the National Cancer Institute, Bethesda, MD (EL and AS).

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[3] Reprints not available. Address correspondence to ET Jacobs, Mel and Enid Zuckerman College of Public Health, Arizona Cancer Center, University of Arizona, PO Box 245024, Tucson, AZ 85724-5024. E-mail: jacobse@u.arizona.edu.

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fiber/d as a cereal supplement for 3 y (18). Baseline data regarding demographic, medical, and lifestyle characteristics were collected with questionnaires, and dietary habits were assessed with the Arizona Food Frequency Questionnaire (13). Nutrient intakes were calculated by multiplying the frequency of each food item's consumption by the nutrient composition for the age- and sex-specific portion size. A total of 1304 study participants completed the WBF trial by having at least one postrandomization colonoscopy, a diagnosis of colorectal cancer, or both. Compared with the low-fiber supplement, the high-fiber supplement had no effect on the risk of colorectal adenoma recurrence (13). The study was approved by the University of Arizona Human Subjects Committee and local hospital committees, and written informed consent was obtained from each participant before study enrollment.

Polyp Prevention Trial

The PPT was a multicenter study conducted by the National Cancer Institute to determine whether an intervention diet of decreased fat and increased fiber, fruit, and vegetables decreased the risk of adenoma recurrence after 4 y of follow-up in participants who had had a polyp removed (19). For the collection of demographic information, behavioral and clinical characteristics questionnaires were administered at baseline (19). Dietary data were ascertained with the use of a modified Block-National Cancer Institute Food Frequency Questionnaire (20). Participants selected frequency and serving size for each food item, then the frequency of each food item's consumption was multiplied by the nutrient composition for the age- and sex-specific portion size to calculate nutrient intakes. Both the WBF trial and the PPT used US Department of Agriculture food-composition tables to assess dietary fiber. These values for total dietary fiber were obtained by using the Association of Official Analytic Chemists method (21). A total of 1905 participants completed the trial by having any endoscopic procedure after the year 1 colonoscopy or, for subjects who missed the year 1 colonoscopy, any endoscopic procedure performed $\geq$2 y after randomization. No effect of the dietary intervention on adenoma recurrence was observed (14). Written informed consent was obtained from all study participants, and the trial was approved by the Institutional Review Board at the National Cancer Institute and by each participating clinic.

Definition of adenoma recurrence

Both the WBF and PPT study protocols included a colonoscopy at year 1, which were followed by another at year 3 (WBF) or year 4 (PPT). For the current analyses, any adenoma or colorectal cancer that occurred after randomization in either trial was included as a recurrence. We selected this endpoint criterion because not all of the WBF participants had both a year 1 and year 3 colonoscopy, because the guidelines for endoscopy surveillance changed during the course of the study. Note that this classification of adenoma recurrence differs from that used in the original PPT, in which it was defined as an adenoma detected after year 1 of the trial.

Data pooling

Data for the PPT were submitted electronically by the National Cancer Institute to the Arizona Cancer Center for pooling with data from the WBF trial. Checks for accuracy and missing values were conducted for each data set individually. Discrepancies were noted and the submitting investigators were queried to resolve any outstanding issues. Variables from both data sets were assigned common names and, if necessary, converted to common units of measurement. Data from each study site were analyzed individually before pooling. After the data sets were combined, thorough checks were conducted to ensure that the pooled data for each study site were identical to the original data set.

For the purpose of assessing the effect of the dietary intervention from each study on adenoma endpoints in the pooled data set, a dichotomous variable was created with 2 categories: the intervention group and the reference group. The intervention group included those participants in the WBF trial who were assigned to the high-fiber treatment group and received 13.5 g fiber/d as a cereal supplement and those in the PPT who were randomly assigned to adopt a diet that was low in fat and high in fiber, fruit, and vegetables. The reference group consisted of those WBF trial participants who received 2.0 g fiber/d and those in the PPT who were assigned to follow their usual diet.

Statistical analyses

All analyses were completed by using the STATA version 8 statistical software package (Stata Corporation, College Station, TX). Summary data for the baseline characteristics were calculated by using a Student's *t* test for continuous variables and by chi-square analysis for categorical variables.

For the comparison of adenoma recurrence and advanced adenoma recurrence between the intervention and reference groups, unconditional logistic regression models were used to generate odds ratios and 95% CIs for the outcome variables of adenoma and advanced adenoma recurrence. First, baseline characteristics (including age, sex, body mass index, family history of colorectal cancer, presence of colorectal polyps before the qualifying exam, current aspirin use, hormone replacement therapy (HRT) use, current smoking, dietary variables, and baseline adenoma characteristics) were tested with likelihood ratio tests to determine which variables were associated with adenoma or advanced adenoma recurrence; those that were significantly related were included in the final model. These analyses were conducted in the total pooled population as a whole, by sex, and by study and sex. Interaction terms were constructed and evaluated for statistical significance with likelihood ratio tests.

Intake of dietary fiber at baseline was categorized into 4 quartiles based on the distribution of the pooled study population. To examine the effect of baseline fiber intake on the outcome variable of adenoma recurrence, the categorical variable was tested in logistic regression models. The analyses were conducted for the WBF trial and the PPT individually among all participants and stratified by sex. These analyses were then repeated for the pooled study population.

To assess whether the intake of baseline dietary fiber modified the effect of the intervention, odds ratios and 95% CIs were calculated with logistic regression models to test the association between the intervention group and the outcome variable adenoma recurrence within each quartile of baseline fiber intake. These analyses were conducted for the pooled study population as a whole and by sex. Statistical results for all tests were considered significant if the 95% CIs did not include 1.0 or if the *P* value was $\leq$ 0.05.

Table 1
Baseline characteristics of the participants in the Wheat Bran Fiber (WBF) Trial and the Polyp Prevention Trial (PPT)

Characteristic	WBF Trial (n = 1304)	PPT (n = 1905)	P^1
Age (y)	65.9 ± 8.8[2]	61.1 ± 9.9	<0.01
Male [n (%)]	874 (67.0)	1228 (64.5)	0.16
BMI (kg/m^2)	27.4 ± 4.4	27.6 ± 3.9	0.37
White race [n (%)]	1251 (95.9)	1706 (89.6)	<0.01
Family history of colorectal cancer [n (%)][3]	220 (16.9)	511 (26.8)	<0.01
Previous polyps [n (%)][4]	452 (39.2)	334 (17.5)	<0.01
Current aspirin use [n (%)][5]	368 (28.2)	438 (23.0)	<0.01
HRT [n (%)][6]	76 (14.4)	221 (11.6)	0.08
Current smoking [n (%)]	178 (13.7)	253 (13.3)	0.76
Dietary variables[7]			
Energy (kcal/d)	1927.2 ± 699.0	1923.1 ± 582.7	0.86
Fat (g/d)	69.0 ± 13.2	76.3 ± 15.5	<0.01
Fiber (g/d)	21.9 ± 7.0	18.6 ± 7.4	<0.01
Calcium (mg/d)	905.7 ± 287.5	844.1 ± 335.0	<0.01
Folate (mg/d)	328.9 ± 99.1	308.1 ± 103.2	<0.01
Alcohol (g/d)	7.2 ± 14.9	7.7 ± 14.0	0.30
Adenoma characteristics			
Size			
Large, ≥1 cm [n (%)]	593 (45.5)	598 (33.3)	<0.01
>1 polyp [n (%)]	562 (43.1)	971 (51.0)	<0.01
Location [n (%)]			
Distal	701 (54.6)	1030 (55.3)	
Proximal	344 (26.8)	504 (27.0)	
Both	239 (18.6)	330 (17.7)	0.81
Highest histology [n (%)]			
Tubular	842 (69.1)	1351 (77.9)	
Tubulovillous	317 (26.0)	348 (20.1)	
Villous	59 (4.8)	36 (2.1)	<0.01

[1] Calculated by using a Student's t test for continuous variables and chi-squared analyses for categorical variables.
[2] $\bar{x}$ ± SD (all such values).
[3] In one or more first-degree relatives.
[4] History of polyps or adenomas before the qualifying colonoscopy.
[5] Use in the past month for the WBF Trial and current use at baseline for the PPT.
[6] Hormone replacement therapy among women (yes or no) in the past 10 y for the WBF Trial and current use at baseline for the PPT; lower numbers reflect missing data.
[7] All dietary data, except alcohol, are energy-adjusted.

RESULTS

A comparison of baseline characteristics in the WBF trial and the PPT, tested by using chi-square analyses for categorical variables and a Student's t test for continuous variables, is shown in **Table 1**. Participants in the WBF were older, were more likely to be white, and were more likely to be current aspirin users than were those in the PPT. With regard to HRT, more women in the WBF reported receiving HRT ($P = 0.08$); however, the questionnaire for WBF asked about HRT in the previous 10 y, whereas that for the PPT inquired about current use. Those in the WBF trial were less likely to have a family history of colorectal cancer but were more likely to have had colorectal polyps. Participants in the WBF trial reported higher intakes of fiber, calcium, and folate, whereas those in the PPT consumed higher quantities of fat. No differences between the 2 trials were detected for energy intake. With regard to baseline adenoma characteristics, a significantly greater proportion of participants had large adenomas and more than one adenoma in the WBF trial than in the PPT, although there were no differences in the location of the adenomas within the colorectum. Finally, participants in the WBF trial were significantly more likely to have an adenoma with some villous histology at baseline than were those in the PPT.

Overall, as evaluated with logistic regression analyses, there was no effect of treatment group on adenoma recurrence in the pooled WBF and PPT populations (**Table 2**). However, among men in the combined population, those in the fiber intervention group had a significantly lower odds of adenoma recurrence than did the reference group. For women, a nonsignificant, slightly increased odds of adenoma recurrence was detected. The addition of an interaction term for sex and fiber intervention group, evaluated with a likelihood ratio test, showed a statistically significant result ($P < 0.03$). The 3-factor interaction (sex, baseline fiber intake, and treatment group) was also statistically significant ($P < 0.03$), although a 4-factor interaction that also included a variable for study was not ($P < 0.12$). An assessment of the studies individually showed no significant effects of the fiber intervention on either the total population or by sex.

The results of logistic regression analyses for the association between fiber intervention and the recurrence of advanced adenomas, defined for the current analyses as adenomas with a villous component or a size of ≥1 cm, or both, are presented in **Table 3**.

Table 2
Odds ratios (and 95% CIs) for colorectal adenoma recurrence in the intervention group in the Wheat Bran Fiber (WBF) Trial, the Polyp Prevention Trial (PPT), and both trials combined, stratified by sex

	Both trials (n = 3209)		WBF Trial (n = 1304)		PPT (n = 1905)	
	Reference (n = 812/1531)[1]	Intervention (n = 854/1678)	Reference (n = 299/584)	Intervention (n = 340/720)	Reference (n = 513/947)	Intervention (n = 514/958)
Both sexes (n = 3209)						
Crude	0.92 (0.80, 1.06)		0.86 (0.69, 1.07)		0.98 (0.82, 1.17)	
Adjusted[2]	0.91 (0.78, 1.06)		0.80 (0.62, 1.03)		0.97 (0.80, 1.17)	
Men (n = 2102)						
Crude	0.81 (0.68, 0.96)		0.78 (0.60, 1.03)		0.84 (0.67, 1.06)	
Adjusted[2]	0.81 (0.67, 0.98)		0.77 (0.56, 1.05)		0.83 (0.65, 1.06)	
Women (n = 1107)						
Crude	1.12 (0.88, 1.42)		1.00 (0.68, 1.48)		1.21 (0.89, 1.65)	
Adjusted[2]	1.13 (0.87, 1.48)		0.87 (0.55, 1.40)		1.27 (0.92, 1.77)	
P for interaction[3]	0.03					

[1] Number of participants with recurrences/total number of participants in the treatment group.
[2] Adjusted logistic regression models include age, BMI, sex (for total population only), family history of colorectal cancer, dietary calcium, alcohol intake, study, history of previous polyps, number of colonoscopies, number of adenomas at baseline, largest adenoma at baseline, and location of adenomas at baseline.
[3] For sex and treatment group, tested with the likelihood ratio test. The interaction of sex, baseline fiber intake, and treatment group was statistically significant, $P < 0.03$.

The adjusted odds ratios for the fiber intervention in the total population and in men and women separately were not statistically significant. Although the results were not statistically significant, the direction of the effect for men and women was the same as that observed for total adenoma recurrence. No significant study-specific associations for fiber intervention group and advanced adenoma recurrence were shown.

As shown in **Table 4**, baseline fiber intake was not associated with adenoma recurrence in the total population, as evaluated with logistic regression models. No significant relations were observed by sex in the pooled population. For the WBF trial, higher baseline fiber intake was associated with a significantly reduced risk of adenoma recurrence in the men. No significant associations were observed for women in the WBF trial or for any analyses of baseline fiber in the PPT. Further analyses of baseline fiber intake by source (grains compared with fruit and vegetables) showed no significant effects (data not shown).

Crude and adjusted odds ratios from logistic regression analyses for the effect of intervention group compared with the reference group on adenoma recurrence, within each quartile of baseline fiber intake, are shown in **Table 5**. Among the pooled population, there were no significant effects of the intervention by quartile of baseline fiber intake. For men, a significantly protective effect was observed for the intervention group in the highest quartile of baseline fiber intake only, whereas no significant association was detected for women.

In an attempt to further clarify the observed sex differences, we tested the effect of HRT on adenoma recurrence in the women from our pooled population to determine whether it modified the effect of the fiber intervention. A nonsignificant decreased odds of recurrence was detected among the women who received HRT; however, the effect of the fiber intervention did not vary by HRT status (data not shown).

Table 3
Odds ratios (and 95% CIs) for advanced adenoma recurrence in the intervention group in the Wheat Bran Fiber (WBF) Trial, the Polyp Prevention Trial (PPT), and both trials combined, stratified by sex[1]

	Both trials (n = 1591)	WBF Trial (n = 598)	PPT (n = 993)
Both sexes (n = 1591)			
Crude	0.97 (0.77, 1.20)	1.05 (0.75, 1.47)	0.87 (0.65, 1.18)
Adjusted[2]	0.94 (0.75, 1.19)	1.06 (0.75, 1.50)	0.85 (0.63, 1.18)
Men (n = 1147)			
Crude	0.89 (0.69, 1.16)	0.98 (0.66, 1.45)	0.80 (0.56, 1.14)
Adjusted[2]	0.85 (0.64, 1.12)	0.96 (0.64, 1.45)	0.76 (0.53, 1.11)
Women (n = 444)			
Crude	1.17 (0.56, 1.78)	1.26 (0.67, 2.39)	1.09 (0.62, 1.91)
Adjusted[2]	1.19 (0.76, 1.86)	1.12 (0.57, 2.20)	1.21 (0.65, 2.23)
P for interaction[3]	0.22		

[1] Advanced adenoma recurrence defined as an adenoma with villous component or a size of ≥1 cm, calculated with logistic regression models.
[2] Adjusted models include age, number of colonoscopies, study, and number of adenomas at baseline.
[3] For sex and treatment group, tested with a likelihood ratio test. All possible main effects, 3-factor interactions, and 2-factor interactions were also tested; none were found to be statistically significant, except for the main effect of trial ($P < 0.001$).

Table 4
Odds ratios (and 95% CIs) for adenoma recurrence associated with quartile of baseline fiber intake in the Wheat Bran Fiber (WBF) Trial, the Polyp Prevention Trial (PPT), and both trials combined, stratified by sex[1]

Median fiber intake (g/d)	Both trials (n = 3209)	WBF Trial (n = 1304)	PPT (n = 1905)
Both sexes (n = 3209)			
12.3	1.00	1.00	1.00
16.8	0.85 (0.68, 1.06)	0.65 (0.42, 1.02)	0.92 (0.71, 1.19)
21.1	1.03 (0.82, 1.29)	0.79 (0.51, 1.23)	1.11 (0.84, 1.46)
28.0	0.86 (0.68, 1.08)	0.58 (0.38, 0.91)	1.03 (0.77, 1.38)
Men (n = 2102)			
12.3	1.00	1.00	1.00
16.8	0.85 (0.66, 1.11)	0.57 (0.33, 0.97)	0.96 (0.70, 1.32)
21.1	1.11 (0.84, 1.47)	0.79 (0.46, 1.35)	1.20 (0.85, 1.69)
28.0	0.80 (0.60, 1.06)	0.44 (0.26, 0.75)	1.07 (0.74, 1.54)
Women (n = 1107)			
12.3	1.00	1.00	1.00
16.8	0.86 (0.58, 1.27)	0.92 (0.38, 2.20)	0.83 (0.53, 1.30)
21.1	0.89 (0.60, 1.31)	0.83 (0.37, 1.88)	0.94 (0.59, 1.51)
28.0	0.98 (0.65, 1.45)	1.10 (0.49, 2.50)	0.94 (0.58, 1.52)
P for interaction[2]	0.37		

[1] Values for adenoma recurrence were calculated with logistic regression modeling and with quartile of baseline intake as the independent variable. The models were adjusted for age, BMI, sex (for total population only), family history of colorectal cancer, dietary calcium, alcohol intake, study (for total population only), number of colonoscopies, intervention group, history of previous polyps, number of adenomas at baseline, largest adenoma at baseline, and location of adenomas at baseline.

[2] For sex and quartile of baseline fiber intake, tested with a likelihood ratio test with 3 df. The interaction term for treatment group–by-sex was statistically significant ($P < 0.03$). A 3-factor interaction term for sex, baseline fiber intakes and treatment group was also statistically significant ($P < 0.03$).

DISCUSSION

The current study was conducted to determine whether there was a differential response by sex to the interventions administered in the PPT and WBF trial. After pooling the data from the 2 trials, we confirmed that men in the intervention group had a significantly reduced odds of adenoma recurrence, whereas no significant effect was observed for women.

Evidence in the literature indicates that fiber may have different effects on the colon, depending on sex. The Nurses Health Study showed no protective effect of fiber among a cohort of 88 757 women, although the medians for the lowest and highest quartiles of fiber intake in this group varied by a factor of 2.5 (12). Among women in the Breast Cancer Detection Demonstration Project, no significant association between total dietary fiber intake and colorectal cancer was shown (10). Only one prospective analysis conducted in women ascertained a significant protective effect of whole-grain fiber on colon cancer (22). Prospective investigations conducted among men and women combined

Table 5
Odds ratios (and 95% CIs) for a comparison of adenoma recurrence between the intervention group and the reference group within each quartile of baseline fiber intake in the pooled Wheat Bran Fiber Trial and Polyp Prevention Trial study populations

	Median baseline fiber intake (g/d)				P for trend[1]
	12.3	16.8	21.1	28.0	
Both sexes					
n[2]	440/803	402/802	425/802	399/802	
Crude	0.94 (0.71, 1.24)	0.93 (0.70, 1.23)	1.11 (0.84, 1.47)	0.75 (0.57, 0.99)	0.40
Adjusted[3]	0.95 (0.70, 1.30)	0.85 (0.62, 1.17)	1.14 (0.84, 1.57)	0.79 (0.59, 1.08)	0.36
Men					
n[2]	340/561	299/539	306/517	259/485	
Crude	0.94 (0.67, 1.32)	0.76 (0.54, 1.08)	0.94 (0.66, 1.34)	0.65 (0.45, 0.94)	0.36
Adjusted[3]	0.87 (0.60, 1.28)	0.73 (0.50, 1.07)	0.97 (0.65, 1.45)	0.64 (0.43, 0.95)	0.21
Women					
n[2]	100/242	103/263	119/285	140/317	
Crude	0.98 (0.59, 1.64)	1.15 (0.70, 1.88)	1.52 (0.94, 2.44)	0.91 (0.58, 1.42)	0.45
Adjusted[3]	1.20 (0.67, 2.13)	1.11 (0.63, 1.98)	1.41 (0.83, 2.41)	1.10 (0.65, 1.84)	0.51

[1] Calculated by using likelihood ratio tests. No statistically significant trends were observed, although the 3-factor interaction for sex, baseline fiber intake, and treatment group and the 2-factor interaction for treatment group and sex were significant ($P \leq 0.05$).

[2] Number of participants with recurrences/total number of participants for the quartile.

[3] Adjusted for age, BMI, sex (for total population only), family history of colorectal cancer, dietary calcium, alcohol intake, study, history of previous polyps, number of colonoscopies, number of adenomas at baseline, largest adenoma at baseline, and location of adenomas at baseline.

(15, 16, 23), or among men alone (9), were more likely to show a protective effect of fiber on colorectal neoplasia, although one recent study did not (24). For example, a large prospective study of men from the Health Professionals Follow-Up Study found a significant protective effect of fruit fiber and soluble fiber intakes against adenoma (9), and a recent prospective study indicated that cereal fiber was associated with a lower risk of advanced colorectal neoplasia in a primarily male population (23). The results from the European Prospective Investigation into Cancer and Nutrition and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial also provided evidence that fiber is protective against colorectal cancer (16) and adenomas (15) in populations of men and women, although sex-specific differences were not observed. In contrast, ≥3 clinical trials failed to observe a protective effect of fiber interventions on colorectal adenomas in study populations comprised of men and women (11, 13, 14), including the WBF trial and the PPT. Only after stratification by sex did the protective effect of fiber against colorectal neoplasia become apparent in the current analysis.

The reasons for differences in response to fiber by sex are unknown. Studies have indicated that HRT in postmenopausal women is protective against colorectal neoplasia (25, 26). It has been suggested that dietary fiber reduces estrogen concentrations in women (27–29); thus, supplementing women with dietary fiber might actually be unfavorable for colorectal neoplasia if estrogen is indeed protective. Although we had only a crude measure of HRT use, we did not detect any modification of the association between fiber intervention and adenoma recurrence by use of HRT (data not shown).

Another possibility is the observed differences in colonic location of polyps and tumors between men and women. McCashland et al (30) used data from the Clinical Outcomes Research Initiative to evaluate sex differences in polyp location and found that women were more likely than men to develop pure right-sided (proximal) polyps. It is possible that dietary fiber is more effective in preventing the recurrence of left-sided (distal) polyps, although the opposite has been argued for fermentable fibers (10). Several of the prospective studies discussed herein suggest either stronger or exclusive protection of dietary fiber for distal lesions (9, 15, 16, 22); however, in some cases, proximal lesions were not evaluated. Both of the clinical trials evaluated in the current analyses suggested that participants in the fiber intervention groups had fewer recurrences in the distal colon than in the reference groups (13, 14). However, we conducted analyses to test the association between fiber intake and adenoma location and found no statistically significant effects (data not shown).

With regard to the association between baseline fiber intake and colorectal adenoma recurrence, there were differences between the WBF trial and the PPT. Men in the WBF trial exhibited a statistically significant reduced risk of recurrence, particularly in the highest quartile of intake, whereas the results for those in the PPT were null. The Arizona Food Frequency Questionnaire, used for dietary measures in the WBF trial (13), was slightly modified from the Block questionnaire used for the PPT (20). Therefore, the instruments were similar and we would expect that the baseline measures of fiber intake would be measured with similar accuracy. Those in the WBF trial did consume significantly higher amounts of dietary fiber at baseline than did those in the PPT, so it is possible that a higher usual intake of fiber is required for beneficial effects in the colorectum.

We did not observe an association between the fiber interventions and recurrence of advanced colorectal adenomas for either sex. Our results agree with those of Lieberman et al (23), who reported no association between total fiber intake and prevalence of advanced neoplasia. In contrast, results from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial showed a significant trend for protection from advanced adenoma for both sexes combined ($P = 0.03$) (15). Because advanced lesions accounted for ≈12% of recurrences in the WBF trial and the PPT, it is possible that we had insufficient power to detect a significant difference.

Potential limitations of the current work include the combination of data from 2 clinical trials in which different interventions were used. The WBF trial compared the effects of a high-fiber cereal supplement (13.5 g/d) with those of a low-fiber supplement (2.0 g/d) (13), whereas the PPT compared the effects of decreased dietary fat intakes and increased intakes of fiber, fruit, and vegetables with those of a habitual diet (14). Therefore, when the intervention groups were combined, we could not rule out the potential effects that the low-fat component of the PPT intervention may have had on these results. Of interest was the observation that the participants in the WBF trial also significantly decreased their fat intakes over time, although this was true in both the high-fiber and low-fiber groups (31). Finally, we could not rule out the possibility that the observed difference between sexes was a chance finding of subgroup analyses.

The strengths of this investigation included the large sample size afforded by pooling 2 large clinical intervention trials. Although each trial individually suggested a sex effect for the intervention groups, pooling the 2 studies allowed for increased precision of the point estimates. Both studies were carefully conducted clinical trials that used similar food-frequency questionnaires and follow-up methods. In addition, both trials were prospective in nature and had minimal loss-to-follow-up of study participants.

In summary, the results of the current study show that men who were randomly assigned to a diet high in fiber, low in fat, or both had a significantly decreased risk of colorectal adenoma recurrence, whereas no effect was detected for women. Although the mechanism by which these differential effects occur remains unclear, future investigations should include stratified sex analyses as well as further study of the effect of fiber on specific colon locations.

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ETJ conducted most of the statistical analyses and data interpretation and prepared the manuscript for publication. EL contributed to the conception and design of the study, supplied ETJ with statistical data for the PPT, participated in each step of the analyses for the study, and contributed to the interpretation of the data. DSA was the Principal investigator for the WBF trial, the population of which was used in this study, and contributed to the interpretation of the findings. C-HH and RJ assisted with the statistical analyses and participated in the discussions of the results. Dr. Schatzkin is the Principal Investigator of the Polyp Prevention Trial, which supplied data for the participants in this study, and contributed to interpretation of the data. PAT participated in weekly discussions of the study results and their interpretation. MEM oversaw each step in the planning and analysis of the study and the preparation of the manuscript. All authors reviewed the final manuscript before submission and none had a conflict of interest with regard to this work.

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